Dynamic and not static change in ventricular repolarization is a substrate of ventricular arrhythmia on chronic ischemic myocardium

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Abstract

Objective: The restitution mechanism has been the focus of attention as the possible mechanism behind ventricular fibrillation (VF). However, its contribution in chronic ischemic heart has not been established. Methods: We investigated chronic ischemic dogs with occlusion of left anterior descending artery. Sixty unipolar electrograms were simultaneously recorded from an entire cardiac surface. Activation-recovery intervals (ARIs) and QRST deflection area (AQRST) were measured during constant atrial pacing. The ischemic dogs were divided into two groups, five dogs in VF(+) group or seven dogs in VF(−) group, according to VF occurrence by programmed electrical stimulation. Results: When investigating ARI dispersions on an epicardium, there was no difference between VF(+) and VF(−) groups. The relationship between ARIs and diastolic intervals was quantified as an electrical restitution curve. The slopes of the ARI restitution curve for the anterior left ventricle in VF(+) dogs were significantly steeper than those of VF(−) dogs. The amplitude of AQRST alternans were significantly greater in VF(+) dogs than VF(−) dogs. Conclusions: Combined observation of steep restitution slopes and increased electrical alternans supported the restitution mechanism as being involved in the arrhythmia. Dynamic restitution properties and not static single-beat ARI dispersion may play an important role in the VF arrhythmia in the chronic ischemic heart.

Keywords: Ischemia; Myocardial infarction; Tachyarrhythmia; Electrophysiology

1. Introduction

Ventricular arrhythmia is a significant contributor to sudden death in patients with chronic myocardial ischemia. In the last decade, the spatial dispersion of QT intervals \cite{1–3} or activation-recovery intervals (ARIs) \cite{4}, reflecting inhomogeneous ventricular recovery, has been widely investigated as a predictor of ventricular fibrillation (VF). However, recently Zabel et al. \cite{5} reported in a larger population study that QT dispersion does not contribute significant information for establishing a prognosis. After their study, the limitation of a static estimation of dispersed repolarization measured in a single beat was recognized.

The restitution mechanism has been the focus of attention as the mechanism determining the transition of tachycardia to ventricular fibrillation \cite{6–8}. The restitution of electrical recovery represents the dynamic beat-to-beat relationship between diastolic interval (DI) and action potential duration (APD) in the heart. The relationship between ARIs and DIs can be quantified as an electrical restitution curve. When the slope of the curve is steep, the small changes of DI cause the large changes in APD and lead to excitation wave instability, such instability is undoubtedly substrates of ventricular tachyarrhythmia \cite{7,8}. The restitution slope, an index of dynamic dispersion of electrical recovery, may be a candidate index predicting arrhythmia vulnerability.

However, the role of the restitution relationship in ventricular fibrillation has not been investigated on the entire ventricles in chronic ischemic myocardium. The purposes of the present study are to investigate the role of...
the mechanism of dynamic changes in repolarization in ventricular fibrillation in chronic ischemic heart. The present study may provide information on the mechanism of this life-threatening arrhythmia in ischemic heart disease.

2. Materials and methods

The investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health. Twenty-four adult mongrel dogs were anesthetized by intravenous administration of sodium pentobarbital (30 mg/kg body wt.), intubated and ventilated with a constant-volume ventilator. ECG (lead II) was monitored continuously. Under aseptic conditions, a left fifth intercostal space thoracotomy was performed and the pericardium was opened. In 16 dogs, the left anterior descending coronary artery at the level just distal of its first diagonal branch was permanently occluded. Another eight dogs that underwent sham operation of the left coronary served as a control group. Dogs were then treated with antibiotics: oral administration of cefcapene pivoxil hydrochloride 200 mg/day for 2 weeks.

Four weeks after the procedure, the dogs were anesthetized again. The heart was exposed by thoracotomy and suspended in a pericardial cradle. The sinus node was crushed, and a bipolar stimulating electrode was attached to the right atrium. The heart was paced at a cycle length of 200–600 ms with 2 ms duration square-wave stimuli at twice diastolic threshold intensity. Sixty silver wire unipolar electrodes attached to a nylon stocking that was stretched over the heart were used for recording cardiac surface electrograms [9,10]. Sixty electrodes were arranged into 10 columns (Fig. 1A). Body temperature was maintained above 36.5 °C by a heating pad with measurement by rectal thermometer. To maintain the temperature and humidity, the thoracic cavity was covered with plastic wrap while recording the electrograms. A polyethylene catheter was placed into a femoral vein and physiological saline solution was infused at a constant rate. An arterial line was inserted into the right femoral artery to continuously monitor the mean arterial pressure. The electrocardiogram lead II and blood pressure were monitored throughout the study on a model 2G66 recorder (NEC San-Ei, Tokyo, Japan).

An additional four dogs with 4-week LAD-occlusion were investigated to evaluate the restitution properties on both epicardial and endocardial sites. We simultaneously recorded six epicardial electrograms and the corresponding six endocardial electrograms of leads A3, B3, C3, D3, E3 and F3 shown in Fig. 1. The form of epicardial electrodes were the same as described above. The endocardial electrodes were unipolar and constructed by 0.1-mm diameter coated wire and 1-mm hook electrodes on the tip. Each endocardial electrode was inserted into the ventricular cavity through the 0.4-mm diameter sheath and hooked on the endocardium, after which the sheath was removed. Data processing of endocardial electrograms were the same as epicardial electrograms, as described in next section.

2.1. Recording of electrograms

Our system [9,10] consisted of the following components: (1) an input box with a total of 64 buffer preamplifiers; (2) a main unit with multiplexing modules, an analog-to-digital converter, a central processing unit (CD-G015, Chunichi Denshi, Nagoya, Japan); and (3) a personal computer (PC-9801, NEC, Tokyo, Japan). Each cardiac surface electrode was referenced to a Wilson’s central terminal. All 60-lead electrograms were recorded simultaneously with a sampling interval of 1 ms. By the use of the CD-G015 system, epicardial mapping data were sampled for 30 s, and the data were transmitted to the personal computer and stored on hard disk, then copied to an MO disc.

2.2. Data processing

Activation-recovery interval (ARI) was defined as the interval between the minimal derivative in the QRS com-
plex and the maximum derivative in the T wave. ARI is known to be a faithful measure of the APD\textsuperscript{[11,12]}. The QRST deflection area (AQRST), the sum of all positive and negative potentials from QRS onset to the end of T deflections, was also calculated. The QRST deflection area represents local recovery properties and its changes are independent of changes in depolarization\textsuperscript{[13]}.

The relationship between the ARI and the diastolic interval (DI) was examined during atrial pacing with cycle lengths of 800–300 ms in step of 100 ms decrement and from 300 ms to the Wenckebach block in steps of 10–20 ms. The relationship between ARIs and DIs is shown in the following function: \( ARI = b(1 - e^{-aDI}) \), to quantify them as an electrical restitution curve. The slopes of ARI restitution curves were measured for each epicardial lead (Fig. 1B).

The susceptibility of ventricular arrhythmia was investigated by programmed stimulation. The ventricular effective refractory period was determined by use of a driving train (S1) of 10 beats with a cycle length of 400 ms, followed by an extrastimulus (S2) that was decremented in 10-ms intervals. The ventricular effective refractory period was defined as the longest S1S2 interval at which S2 failed to elicit ventricular activation. The second extrastimulus (S3) was started with the S1S2 interval fixed at 40 ms longer than the ventricular effective refractory period. The S2S3 interval decrements until S3 failed to elicit ventricular activation.

2.3. Statistical analysis

Statistical inferences were made by use of the Statistical Analysis System (SAS) program (SAS Institute, Cary, NC). Data are expressed as mean \pm standard deviation. Statistical significance was assessed by analysis of variance (ANOVA) with post hoc Bonferroni tests for multiple comparisons. A confidence level of 95% was considered statistically significant.

3. Results

3.1. Spatial distribution of ARI and ARI dispersion

We divided the coronary-occluded dogs into two groups: five dogs in the VF(+) group and seven dogs in the VF(−) group, according to the occurrence of VF induced by programmed electrical stimulation. Averaged ARI maps of control, VF(+), and VF(−) groups were displayed as an
apical polar projection format as shown in Fig. 2. On the maps, the center represents the apex and the peripheral circle represents the base of ventricles. The upper portion of the circle represents the anterior wall and the lower portion the posterior wall. In VF(+) and VF(/C0) groups, the ARIs tended to be short on the left anterior epicardium, and relatively prolonged on the base of the left ventricle and right ventricle. However, the difference in ARI distribution between VF(+) and VF(/C0) groups was not apparent on the maps. Next, we measured the maximal ARI, minimal ARI and ARI dispersions among all epicardial leads by a conventional method. The results indicated that there was no statistical differences between VF(+) and VF(−) groups in the present study (Table 1). The mean ARI dispersions of VF(+) and VF(−) groups were almost equal, both 55 ± 30 ms.

3.2. Restitution slope

The dynamic restitution relationship was investigated during constant atrial pacing. The maximal slopes of the restitution curve, restitution slopes, were measured on each lead point of a cardiac surface and displayed in a map with apical polar projection. The maps of VF(+) group showed an increased restitution slope on the anterior epicardium (Fig. 3). The maximal value was 0.75. In contrast, the map of the VF(−) group was uniform and the values were low; the maximal value was 0.41. In control dogs, the slopes were also uniform and low.

The restitution slope was statistically compared between VF(+) and VF(−) groups. The shaded area in Fig. 4 indicated the epicardial areas where restitution slopes were significantly steeper in the VF(+) group than in the VF(−) group.

Table 1
Maximal ARI, minimal ARI and dispersion of ARIs in control, VF(−) and VF(+) groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Ischemia</th>
<th>VF(−)</th>
<th>VF(+)</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>8</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Maximal ARI</td>
<td>201.9 ± 11.9</td>
<td>189.1 ± 18.3</td>
<td>209.6 ± 16.0</td>
<td></td>
</tr>
<tr>
<td>Minimal ARI</td>
<td>162.1 ± 9.8</td>
<td>133.9 ± 31.3*</td>
<td>154.4 ± 27.4</td>
<td></td>
</tr>
<tr>
<td>ARI dispersion</td>
<td>36.8 ± 7.8</td>
<td>55.3 ± 29.5</td>
<td>55.2 ± 30.3</td>
<td></td>
</tr>
</tbody>
</table>

Values were presented means ± standard deviation. N, number of studied dogs; VF(−), coronary-occluded dogs without induced VF; VF(+), coronary-occluded dogs with induced VF; VF, ventricular fibrillation; ARI, activation-recovery interval.

*p < 0.05 vs. control.

Fig. 3. Group average ARI restitution maps of control, VF(+) andVF(−) dogs. ARI restitution slopes of all 60 leads were displayed in an apical polar projection of ventricles. In VF(+) group, restitution slopes were steep on the anterior infarcted lesion. LV, left ventricle; RV, right ventricle; ARI, activation recovery interval; VF, ventricular fibrillation.
group. The map indicated that restitution slopes were significantly steeper in the VF(+) group compared with the VF(−) group on the LV anterior wall.

The restitution properties were evaluated on both epicardial and endocardial sites. Although it was limited in studied number and not statistically significant, the restitution slope tended to be greater in the endocardial sites than in the epicardial sites in infarcted or non-infarcted region (Fig. 5).

3.3. Alternans in QRST deflection area

The linkage of electrical restitution and the electrical alternans is a key process of the induction of VF. Therefore, beat-to-beat changes in AQRST on a cardiac surface were analyzed. In a representative case (Fig. 6), the AQRST revealed the lasting fluctuations during a rapid atrial drive. In the case of the VF(+) group, the oscillation appeared to be an alternans at a cycle length of 240 ms. The maximal amplitude of AQRST oscillation of all epicardial sites was compared among control, VF(+) and VF(−) groups (Fig. 7). The amplitude of AQRST oscillation was significantly greater in the VF(+) group than the VF(−) group.

4. Discussion

4.1. Major findings

In the present study, slopes of the restitution relationship were measured from the entire epicardial surface of chronic ischemic myocardium. The maximal slopes of the ARI restitution curve on the anterior left ventricle in VF(+) dogs were significantly steeper than those of the VF(−) or control dogs. The amplitude of AQRST alternans was significantly greater in the VF(+) group than the VF(−) group. Combined observation of steep restitution slopes and increased electrical alternans supported the restitution mechanism as being involved in the arrhythmia. Since dispersion of ARIs did not differ between the two groups, restitution properties may play an important role in the occurrence of VF in chronic ischemic myocardium. This is the first evidence that dynamic restitution property and not static repolarization dispersion in a single beat affects the induction of VF in chronic myocardial ischemia.
4.2. Static dispersion in action potential duration

Heterogeneous action potential duration in the myocardium, i.e. APD dispersion, has been thought of as a substrate of the ventricular arrhythmia. The excitation waveform coming though the short-APD myocardium was blocked in the myocardium with incomplete recovery in the long-APD myocardium and resulted in the wavebreak. Many previous experimental studies have demonstrated the relationship between an increased heterogeneity in repolarization and arrhythmogenicity [15,16]. Moreover, several clinical studies about the QT [1–3] or ARI dispersion [4] identify the dispersion in recovery as a predictor of ventricular arrhythmia. However, recently, Zabel et al. [5] indicated that QT dispersion failed to predict a risk such as mortality or arrhythmic events in 280 patients with myocardial infarction. Brendorp et al. [14] also concluded that QT dispersion has no prognostic information for 1319 patients with heart failure. The present study also supported these conclusions, since ARI dispersion did not differ between VF(+) and VF(−) groups. The results may suggest the limitation of the static measure of heterogeneity in repolarization in a single beat and suggest investigating the role of beat-to-beat change of recovery electrophysiology on the occurrence of ventricular arrhythmias. Measuring recovery properties on the multiple beats with various cycle lengths might provide more important information about the heterogeneity in repolarization and ventricular arrhythmia than measuring single-beat recovery properties.

4.3. Restitution hypothesis on VF induction in ischemic heart

In the present study, dynamic relationships between diastolic intervals and action potential duration, i.e. the restitution properties, were examined in the chronic ischemic myocardium. The results indicated that the restitution slope in the dogs with inducible VF were significantly steeper in those without inducible VF.

Recently, restitution properties have focused attention on the transition to ventricular fibrillation (the restitution hy-

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**Fig. 6.** The representative trace of AQRST alternans. The value indicated the beat-to-beat AQRST data on the left anterior epicardium (lead E5). In case of VF, the amplitude of QRST alternans appeared to be greater in pacing with cycle length 240 ms. VF, ventricular fibrillation. AQRST, QRST deflection area.

**Fig. 7.** The group average amplitude of AQRST oscillation. The maximal amplitude of AQRST oscillation of all epicardial sites was compared, among control, VF(−) and VF(+) groups. The amplitude of AQRST oscillation significantly increased in VF(+) in pacing with cycle length of 240, 300 and 400 ms. VF, ventricular fibrillation; AQRST, QRST deflection area; *p < 0.05; **p < 0.01.
electrophysiological response, especially in I. In the present study, we used a parameter, AQRST, as an index of alternans. Ohara et al. [17] showed that steep restitution properties altered the reentry sequence during VF and increased the wave break in the border zone of myocardial infarction. The present observation that VF occurred with a steeper restitution slope also showed that steep restitution properties altered the development of ventricular fibrillation. Ohara et al. [17] described the steep restitution on the border zone between chronic infarcted myocardium and normal myocardium. We also observed the steep restitution slope in the chronic ischemic area. The reason for the discrepancy was not clear, but it could be speculated that it is due to the difference in degree and combination of alteration of channel function, such as \( I_{K_{K}}, I_{K_{S}}, I_{o} \) or \( I_{K_{ATP}} \), in ischemic and healed regions. The mechanism of electrical remodeling is still a major, unresolved question, including the mechanism of alteration of the restitution properties. To answer this question, further studies will also be required.

In conclusion, dynamic dispersion of the electrical recovery may play an important role in the arrhythmogenicity in the chronic ischemic heart. However, the underlying mechanisms forming the steep ARI restitution in ischemic heart remain undefined. Further studies will also be required to address this point.

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